

REMARKS

Claims 1-9, 13, 15, 18-25, 58, 97, 125, and 262-307 are pending in the subject application. By this amendment, Claims 1-2, 4, 6-9, 24-25, 58, 97, 125, 262-265, 269, 273-284, 289 and 294-303 have been amended. Applicants maintain that the amendments do not raise an issue of new matter. Support for the amendments can be found at least in the previous version of the claims and in the specification as filed (WO 03/061363) in the paragraph spanning pages 10-11, the 1st paragraph on page 24, and the 1st paragraph on page 33. Accordingly, entry of the amendments is respectfully requested.

Rejections under 35 U.S.C. §103(a)

Claims 1-4, 6-9, 13, 15, 19-22, 24-25, 58, 97, 125, 262-272, 276-284 and 287-307 stand rejected as being unpatentable over Wabl et al., U.S. Patent 5,885,827 (“Wabl”) in view of Muramatsu et al., *Cell*, 102: 553-563 (2000) (“Muramatsu”).

Claims 5 and 23 stand rejected as being unpatentable over Wabl in view of Muramatsu, and further in view of Wang et al., U.S. Patent Application Publication No. 2003/0119190 (“Wang”).

Claims 273, 274 and 275 stand rejected as being unpatentable over Wabl in view of Muramatsu, and further in view of Griffiths et al., U.S. Patent 5,885,793 (“Griffiths”).

Claims 18, 285 and 286 stand rejected as being unpatentable over Wabl in view of Muramatsu, and further in view of Honjo et al., U.S. Patent 6,815,194 (“Honjo”).

Applicants respectfully traverse these rejections for the reasons set forth below.

For subject matter defined by a claim to be considered obvious, the Patent Office must demonstrate that the differences between the claimed subject matter and the prior art “are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.” 35 U.S.C. § 103(a); see also *Graham v. John Deere Co.*, 383 U.S. 1, 148 U.S.P.Q. 459 (1966). The ultimate determination of whether an invention is or is not obvious is based on certain factual inquiries including: (1) the scope and content of the prior art, (2) the level of ordinary skill in the prior art,

(3) the differences between the claimed invention and the prior art, and (4) objective evidence of nonobviousness. *Graham*, 383 U.S. at 17-18, 148 U.S.P.Q. at 467.

Applicants maintain that consideration of the aforementioned Graham factors indicates that the present invention, as defined by the pending claims, is not obvious in view of the cited references.

Regarding the scope and content of the prior art, Wabl discloses a method of performing random mutagenesis of a heterologous target gene using the immunoglobulin hypermutation system. In particular, the method involves transfecting an immunoglobulin-mutator-positive cell with a hypermutation-competent expression vector into which has been cloned a target gene, and allowing the target gene to hypermutate. Wabl defines a “mutator positive cell line” as a cell line containing cellular factors that work in combination with enhancers to induce hypermutation.

Muramatsu discloses that overexpression of activation-induced cytidine deaminase (AID) in a lymphoma cell line augments antibody class switching from IgM to IgA without cytokine stimulation. Muramatsu also discloses the generation of AID-deficient mice. AID deficiency completely blocked class switch recombination (CSR) in B cells activated by lipopolysaccharide (LPS) *in vitro* and by antigens *in vivo*. In addition, Muramatsu demonstrates that B cells isolated from AID-deficient mice are defective in somatic hypermutation. Based on these results, Muramatsu states that it is “unexpected” that a mutation in AID abolishes both CSR and hypermutation, and hypothesizes that AID is an RNA editing enzyme that requires a co-factor for its activity (Muramatsu reference at page 560, first column, and page 561, first column).

Wang discloses a random mutagenesis system wherein a non-oncogenic, replicating vector acts as a vehicle to randomly introduce a construct comprising a hypermutation-inducing element into the genome of a host cell. Introduction of the hypermutation element in the host cell genome induces mutations (e.g., point mutations, small deletions, and/or small insertions) in genes adjacent to the integrated hypermutation element.

Griffiths discloses a method of isolating antibodies directed against self antigens using phage display technology.

Honjo discloses the amino acid sequences of mouse and human AID proteins.

For purposes of the present analysis, one of ordinary skill in the art can be assumed to be a person with an advanced degree and experience in the relevant art.

Applicants maintain that neither Wabl nor Muramatsu disclose or suggest that AID causes mutations by deaminating DNA, as required by the amended claims. Indeed, applicants maintain that the precise mechanism of action of AID was unknown in the art at the time the priority application was filed. In this respect, and contrary to the allegations of the Office Action, applicants maintain that at the relevant time AID was one of *many* factors suspected to be involved in somatic hypermutation and CSR, and it was not known or suggested that AID alone is sufficient to directly induce the DNA mutations required for somatic hypermutation. Therefore, applicants maintain that one of ordinary skill in the art would not have been motivated to choose AID for the purposes of inducing mutations via deamination of DNA. As such, one of ordinary skill in the art would not have been motivated to combine the disclosures of Wabl and Muramatsu and arrive at the subject matter of the pending claims.

Applicants maintain that none of the secondary references compensate for the deficiencies of Wabl and Muramatsu. In this respect, Wang, Griffiths, and Honjo do not disclose or suggest expressing a transgenic activation induced cytidine deaminase (AID) gene in a eukaryotic cell and expressing the DNA sequence in the cell, wherein AID initiates mutagenesis by deaminating the DNA sequence.

Considering all of the Graham factors together, applicants maintain that it is clear that the present invention would not have been obvious to one of ordinary skill in the art at the relevant time in view of the combination of the cited references. Accordingly, reconsideration and withdrawal of these rejections are respectfully requested.

Applicants: Alberto Martin, et al.
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CONCLUSIONS

In view of the preceding amendments and remarks, applicants respectfully request that the Examiner reconsider and withdraw the rejections in the November 14, 2008 Final Office Action, and earnestly solicit allowance of the claims under examination. If there is any minor matter preventing the allowance of the subject application, the Examiner is requested to telephone the undersigned attorney.

A check for \$470.00 is enclosed for a small entity for the \$405.00 fee for filing a Request for Continued Examination and the \$65.00 fee for a one month extension of time. No other fee is deemed necessary in connection with this reply. However, if any other fee is required to maintain the pendency of the subject application, authorization is hereby given to withdraw the amount of any such fee from Deposit Account No. 01-1785.

Respectfully submitted,

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By


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